EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: BOSTON SCIENTIFIC CORP.,
PELVIC REPAIR SYSTEMS,
PRODUCTS LIABILITY LITIGATION — MDL NO. 2326

THIS DOCUMENT RELATES TO:

KATHERINE L. HALL — 2:12-cv-08186
CAROLYN FRANCES SMOTHERS — 2:12-cv-08016

RULE 26 EXPERT REPORT OF DR. VLADIMIR IAKOVLEV, MD

The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. The opinions which are held and expressed are as follows:

I. QUALIFICATIONS

I am an anatomical pathologist and director of Cytopathology at the Department of Laboratory Medicine, St. Michael's Hospital, Toronto, Canada. I hold an appointment at the Department of Laboratory Medicine and Pathobiology, University of Toronto. My professional activities include diagnostic examination of specimens removed surgically or by biopsies from the human body, where my annual practice volume amounts to 5000 cases. As an academic physician, I pursue research endeavors and teach medical student and residents.

My pathology training was completed at the University of Manitoba Anatomical Pathology residency program, Canada. I hold medical licenses in the province of Ontario, Canada; and the state of Michigan, USA. As a subspecialist anatomical pathologist, I am a fellow of the Royal College of Physicians of Canada and a diplomate of the American Board of Pathology. For research training, I completed the Molecular Oncologic Fellowship Program at the Ontario Cancer Institute, Toronto, Canada. My research focus is in the morphometry, assessment of biomarkers in tissue and analysis of morphological and genomic data. I am specifically interested in spatial (3-dimensional) distributions of biomarkers and structures in the human body. My Curriculum Vitae is attached hereto as Exhibit A.

In 2012, I was approached by Dr. Robert Bendavid, who is a recognized authority and an author of several books and numerous publications in hernia repair. He introduced me to the problems of hernia repair, where the amounting evidence indicates that the use of synthetic mesh is associated with higher rates of late onset postoperative pain, mesh deformity, migration and extrusion. We started a study to investigate the morphological specifics of tissue before and after the inguinal hernia surgery, with and without the use of the mesh. One of the specific approaches was to identify branches of peripheral nerves using dye-labeled antibodies against peripheral

nerves. The method is known as immunohistochemistry, and the stain highlights S100 protein within the Schwann cells (myelin wrapping of the peripheral nerves). Later the project extended to the anterior abdominal wall repairs and our scope expanded into mesh deformities, migration and deformation. I started receiving consultation cases from different parts of North America and these included transvaginally placed meshes. By this date I have examined over 100 specimens. The explanted mesh types included woven, knitted, printed, GoreTex and combined designs of different manufacturers. I also examined new samples for their pre-operative characteristics.

As a non-specific, readily recognized by pathologists and well described in the literature finding, the inserted meshes are surrounded by dense scar and foreign body type granulomatous inflammatory reaction. The scars normally fill or encapsulate damaged tissue or foreign objects in the body. The foreign body type inflammatory reaction is commonly seen when a foreign object or a microorganism is either too large to be absorbed by a single cell, or is too resistant to an action of a single cell. To overcome this, the immune cells, macrophages, join together in a single cell – multinucleated giant cell. This larger merged cells resorb or phagocytise (ingest) the foreign object or bacteria. Examples would be surgical sutures, accidental foreign objects, parasites, TB bacteria. Reaction does not stop until the object is either removed or destroyed.

Although commonly discussed, scarring and granulomatous inflammation represent only a small fraction of the changes initiated by the mesh placemen t into the body. One of our new findings was nerve ingrowth and entrapment in the mesh-scar conglomerate. To investigate the factors affecting the risk of ingrowth we assessed peripheral nerve density in the human tissues. Starting from the lowest in ischemic (blood deprived) tissue it is higher in anterior abdominal wall, then increases laterally (sideways) and lower in the groin and the highest, out of the sites I examined is in the female external genital organs. The ingrowth data showed the nerves regenerate at the same rate after the surgery, either with or without the mesh. Their ingrowth is an opportunistic phenomenon, where the mesh happens to be on the way of regeneration after surgery, or migrates into the nerves.

As I mentioned, the finding expanded beyond peripheral nerve assessment and, in relation to transvaginal placement are organized below in the following order:

1) By complication
Morphological findings related to specific complications (symptoms).

2) By patient
Case based clinico-pathological correlations.

1. FINDINGS IN VIEW OF COMPLICATIONS

I analyzed published literature and records of the patients with transvaginally placed mesh devices. A list of the facts or data considered in forming my opinions is attached hereto as Exhibit B. The complications of the mesh placement into the body can be separated into the following four groups:

1.1 Pain:

acute and chronic, steady and intermittent, sharp and dull, related or not to a movement or activity.

1.2 Urinary symptoms (worsened or appeared after surgery):
dysuria, urgency, incontinence, need to change position to initiate or complete emptying, nocturia.

1.3 Mesh hardening, deformation, formation of nodule/mass.

1.4 Mucosal lesions and/or postcoital bleeding.

1.1 PAIN

Pain is indicated as one of the reasons for explantation for all transvaginal mesh specimens I received (>30). In the records the pain has been described as follows.
By duration:
-sudden and short occurring during a specific movement or activity
-prolonged for a longer period time, either initiated by a movement/activity or not
By onset/chronicity:
-acute, sudden and recurs rarely
-chronic, recurs frequently or constant waxing and waning
By location:
-pelvic, vague
-localized, superficial or deeper
By trigger:
-no trigger
-specific movement, either specific muscle contraction or a specific posture/activity
-activity associated with external pressure, intercourse, palpation, tampon

1.1.1 Vulnerable nerve position

Morphological findings, which can explain pain, are those showing the mechanism of nerve or receptor irritation. The most direct evidence of nerve involvement by the changes related to the mesh placement in the body, is the finding of nerve entrapment or compression either in the mesh structure, mesh-scar conglomerate or their vulnerable position in the superficial submucosa with a hard support. The association of nerve entrapment and compression with pain is well established in medicine and became a common knowledge (herniated disc, nerves circled by sutures, "funny bone" etc.). Since the dawn of surgery the surgical techniques have been developed to avoid nerve damage and entrapment. Specific examples include closure of chest wall, pinning of the bones for external fixation devises, hernia repair, fracture and soft tissue repair, amputation techniques.

The spaces within the mesh structure are not present before surgery, therefore a position of nerves within the mesh indicates ingrowth. Examples of nerve ingrowth into the mesh structure are shown in Figure 1. As mentioned earlier, the female genital area has much higher nerve density compared to the anterior abdominal wall and groin. In our studies nerve ingrowth has been detected in 100% of transvaginal meshes and over 90% of meshes from other sites explanted due to pain. The nerve branches can be also trapped in the scar tissue surrounding the mesh. This can further be complicated by a deformation of the mesh-scar conglomerate (Figure 2). In cases of nerve entrapment, movement or external pressure applied to the tissue deforms or moves the mesh and the force is transferred directly to the nerves. Pain on movement or external pressure can also be due to mesh hardening and attachment to tissue components. In this cases receptors in the pulled

tissue can be irritated. Another vulnerable position of the peripheral nerves is in the upper submucosa, where the nerves are sandwiched between a thin (frequently atrophic) mucosa and hardened irregular mesh-scar plate (Figure 3). A pressure on the mucosa can affect the nerves (intercourse).

1.1.2 Vascular mechanisms

Prolonged pain (hours, days) can have several mechanisms. One of the causes of this type of pain is tissue swelling. In cases of nerve entrapment, tissue swelling can compress the nerves and receptors. Pain due to swelling is present in cases of inflammation (skin pimple, infected wound, gout, etc.) and trauma. The effect is amplified in rigid spaces. Regardless of a trigger, tissue swelling is the result of altered vascular in- and outflow and vascular permeability. Within the meshes, triggering events can be a minor mechanical trauma or inflammation flare. The low pressure outflow vessels (venules and lymphatics) can be compressed by a minor pressure increase within the rigid compartments, which further compromises the outflow and worsens oedema. The most dramatic example of this paradoxical situation is toothache and compartment syndromes when urgent surgical intervention is needed to release the pressure. Within the mesh compartments there are areas of dilated and congested vascular spaces, which indicates stasis Areas of fat necrosis and chronic oedema are seen as well (Figure 4). If the affected compartments contain nerves, these become exposed to compression. This mechanism can result in prolonged pain, which can be recurrent and chronic.

Another type of vascular mechanism of pain in human body is ischemia. The commonly known example is myocardial infarction (heart attack). The arteries require higher external forces to reduce their capacity and the finding of compromised arteries is less frequent in the mesh specimens (~10%), however the finding is focal and is likely underestimated in partially excised devices (Figures 5&6). When present, it can produce significant ischemic pain and lead to tissue necrosis.

1.1.3 Muscle attachment to the mesh

There are two types of muscle fibers in our body, striated (skeletal) and smooth (internal organs and vessels). The striated muscle contracts at our will and provides voluntary movements. It has been found present in three cases of transobturator sling explants. The striated muscle was seen either anchored through the mesh structure or within the scar adjacent to the mesh (Figure 7&8). The mechanism of muscle fibers positioning through the mesh structure is likely complex, when a mesh is placed within, or migrates into the muscle, then the muscle fibers regenerate within the mesh spaces. In the situations when the muscle is either anchored through the mesh or is firmly attached to it by the scar tissue, the muscle contraction results in pulling of the entire mesh. This can produce direct force on the nerve entrapped in the mesh or surrounding scar tissue. This phenomenon can be suspected if a patient complains of pain associated with specific movement (sitting, standing up, ball exercise etc.).

The smooth muscle is present in internal organs and is not consciously controlled (involuntary). Its contraction is regulated by an independent part of the nervous system. In cases of transvaginal meshes, finding of smooth muscle introduces another category of symptoms, urinary.

1.2 URINARY SYMPTOMS

Analysis of the available to me clinical records shows that the urinary symptoms are reported by the most patients, who had complications after implantation of the Boston Scientific devices. These range from periodic dysuria to a more complex problems such as incontinence, incomplete emptying, need to change position to initiate or complete urination, nocturia and frequent bladder infections. The most severe complications are described as erosion through the bladder or urethral wall. Although aimed to prevent or alleviate the symptoms of prolapse, the mesh devices need to counteract the weight of full bladder and/or intra-abdominal pressure. If a mesh is supporting directly either urethra or bladder, the pressure eventually forces it to migrate into the organ wall.

The excised specimens contain thick bundles of smooth muscle, which at the anatomical location indicates bladder wall. The mesh becomes either anchored to the muscle or penetrates deeper and is surrounded by the muscular layer (Figures 9&10). Depending on the degree of involvement, the bladder wall involvement by the mesh can produce symptoms from irritation to interference with muscle function and full penetration through the wall. Additionally, distortion of the bladder can explain the need to change position to initiate or finish emptying.

Additionally, the mesh is seen affecting the neural ganglia within the wall (Figure 11). These neural cells control the bladder muscles, which, depending on location either contract to empty the bladder, or constrict the urethral opening to hold the urine.

1.3 MESH HARDENING, DEFORMATION, MIGRATION AND FORMATION OF A NODULE/MASS

The explanted specimens show consistent hardening, but their degree of visible deformation varies according to a size of the specimens. Some apparently flat portions reveal folding and complex deformations under the microscope. The deformation is not unique for transvaginal devices. In our studies it has been observed commonly in knitted polypropylene meshes. Any deformation is associated with movement of a part of the mesh, therefore migration and deformation overlap. While migration is more dependent on forces external to the mesh, the deformation can be the result of either forces generated within the mesh or forces external to the mesh, or combination of both.

1.3.1 Mesh hardening

All examined explants have been found firmer that the new devices or mesh-free human fibrous and scar tissue. Under the microscope, the mesh filaments are tightly surrounded by the scar tissue. Flexibility and elasticity of a new mesh is dependent on the degree of freedom of the polypropylene filaments within the structure. When the mesh is fully integrated into the scar the degree of mobility of the filaments is dependent on the firmness of tissue within the spaces between the filaments. In all cases these spaces are filled with collagenous scar. At the same time the mesh reinforces the scar like rebar in concrete structures. Most of scar maturation occurs within one year, where new scar tissue can be added at any time if there is a stimulus. In repair processes the degree of scarring correlates with the amount and duration of inflammation. Inflammation in response to introduction of the mesh device is the highest after surgery and subsides with time. The inflammation is uniformly present in all explanted mesh specimens and is present as long as the device remains in the body. Another stimulus for scarring is tissue hypoxia, which has not been studied in meshes. I detected vascular compromise in several specimens. Further hardening of the mesh-scar conglomerate can involve the polypropylene material. Polypropylene changes in the body are discussed below in 1.3.3.

1.3.2 External forces leading to migration and deformation

1.3.2.1. Scar contraction

Maturing scar tissue contracts by the action of myofibroblasts, which can be the source of deformation before the scar matures (approximately 1 year, depending on efficiency of healing).

1.3.2.2. Striated muscle attachment

Striated muscle, if connected to the mesh (Figure 7&8), can be a cause of mesh migration or deformity. The connection was detected in specimens which included striated muscle. Smooth muscle connection is a more frequent finding (Figures 9&10), which also applies a pulling force on the mesh.

1.3.2.3. Tissue pressure and movements acting on the mesh

Soft tissue moves and deforms with normal movements, activities (exercising, sitting, intercourse etc.) and physiological processes (bladder filling and emptying). These movements generate forces acting on the embedded mesh. A repetitive or constant force acting in one direction, can move the mesh and remodel human tissue (similar to orthodontics where small forces move teeth and remodel bones). The movement is easier to observe in larger mesh devices. For example, in our study of larger patches of knitted mesh in the anterior abdominal wall we observed folding with sliding migration of larger parts of the mesh. A transmigration of the sling meshes into the bladder wall is a sign of migration in the transvaginal meshes (Figures 9&10). A migrating mesh is forced to deform if there is a resistance on the path.

1.3.3 Internal Mesh Forces

Curling of the edges of knitted surgical meshes had been noticed since their introduction and the edges were recommended to be secured by stitching for the abdominal wall surgeries. The edges of the transvaginal meshes are not secured and the explanted meshes show curling of the edges (Figure 12). The narrow tapes roll into cord-like structures, which can cut into tissue at higher forces (full bladder). Microscopically, the explanted meshes also show a large array of curling and folding deformations (Figure 13&14). The curling is more visible in a mesh removed with minimal adherent tissue (Figure 15). In the latter example, the symmetry of deformation and the lack of tissue support points to internal forces causing the deformation. These are discussed below.

1.3.3.1 Stretch test

New Boston Scientific sling have been subjected to stretch test to simulate forces acting on the device in the body. The tape was stretched 20% of the original length, after which it showed permanent bowing, lengthening and raised edges. The deformation advanced after repetitive stretching during 30 seconds (Figure 16). The deformation was similar to the naturally occurred deformations shown in Figures 13, 14 &15.

The next step of simulation testing was to reproduce an environment where the tissue supporting mesh return to the original configuration after deformation. An elastic tape was applied on both sides of the mesh sling and all three layers were secured by clamping. The layers were subjected to stretching similarly to the first test. The mesh part did not return to the original length and shape. Its length and deformity forced it into a sinusoidal shape (Figure 17). When the clamps were released, the longitudinal curves were

acting as points of folding (compare with naturally occurred curves and folds in Figure 14).

1.3.3.2 Mesh design

New Boston scientific devices have been examined, including the Uphold and Obtryx. The mesh is knitted, where the structure is formed by loops of a polypropylene filament. The Uphold and Pinnacle devices have the same mesh design with a more complex pattern and the filaments show evidence of heat treatment. The Lynx, Advantage and Obtryx devices share a common mesh tape, which is different from the Uphold and Pinnacle. In this type of mesh, the loops in the knitting structure have the same orientation in a repetitive pattern. All loops bow to one side of the mesh and all loop ends (knots) are facing the other side (Figure 18). The side with knots has greater friction to the touch, while the side with arching loops feels smoother. The mesh is nearly identical to another brand of transobturator tape.

The unidirectional knitting pattern is analogous to the knitting pattern "stockings pattern" used in knitted clothing where all loops come from the same side. The pattern is known to have curling edges. To prevent the edges from curling (edges of sweaters, scarves) a pattern of alternating rows with loops coming from opposite directions is used. The filaments are bent to knit the mesh, which deforms the filament from the original straight shape. A springing, or "plastic memory" force is acting on each loop, which in case of unidirectional patter act in concert in one direction and cause curling. The force is released by pulling in the experimental setting (1.2.3.1). To counteract these forces, mesh is heat treated in the Uphold and Pinnacle devices (Figure 19). The different knitting pattern and heat treatment changes the qualities of mesh and the pattern of deformation after stretching. Note the naturally occurred spiralling direction of deformation in the upper panel of Figure 12.

1.3.2.2 Polypropylene degradation

Several observational and experimental studies showed that polypropylene used in the mesh degrades while exposed to the body environment. Microscopic examination of the explanted meshes shows a layer of homogeneous material at the surface of mesh filaments. The layer stains light-purple by the haematoxylin dye, while the central core of the filaments does not absorb the dye. Also, the material adheres to the glass slide and tissue, while the central core is peeling off the glass surface (Figures 20). To investigate the nature of this material it was examined under polarized light as well as tissue was stained using antibody against myeloperoxidase.

Light polarization is a technique routinely used to identify crystals and foreign material in the tissue. Polarizing filters let light waves of one linear orientation pass through, while block the light waves of other orientation. If two polarizing filters overlap with their orientation perpendicular to each-other, the light is blocked. However, if an object with polarizing properties is placed between the filters, light passing through the object deviates from the blocked perpendicular orientation and becomes visible through the second filter. Under polarized light, both central core of the filament and the outer layer showed the same polarizing properties (Figure 20). This test showed that the layer is synthetic and has optical properties of central polypropylene core. The Uphold type of mesh shows a more brittle nature of the outer "bark" layer (Figure 21).

The next step was to determine if the outer layer is produced during manufacturing

process or forms in the body. Three samples have been compared: unused new mesh, specimen of a patient (#1) with a year of in-vivo exposure; and specimen of a patient, which was explanted after 9 years of in-body exposure (#2). A piece of new mesh had been subjected to the same formalin fixation, chemical processing, paraffin embedding and staining procedures as the two samples from the patients. The new mesh showed no stainable layer; the sample of patient #1 had a thin layer absorbing the stain; while the sample of patient #2 had a detectably thicker layer absorbing haematoxylin dye (Figures 20&22).The thicker layer of degraded polypropylene in case of patient #1 showed cracking at high magnification and peeled off the central core, visually similar to a tree bark. This cross sectional appearance is consistent with earlier reported surface imaging of mesh filaments by scanning electron microscopy

Further proof that the outer layer is synthetic was obtained from immunostaining for myeloperoxidase. Staining for myeloperoxidase showed extra and intracellular positivity with higher density of staining in areas surrounding the mesh. Myeloperoxidase was present immediately at the outer "bark", but not within it (Figure23&24). The presence of myeloperoxidase around the filaments also showed that polypropylene surface is exposed to oxidative environment, which was still present 9 years after surgery.

Transmission electron microscopy (TEM) was used to evaluate the degraded surface at ultra high magnification. This type of EM is similar to conventional light microscopy, except in conventional microscope thin tissue sections are shone light through, while an electron beam is used in TEM to visualize the structures. Vaginal sling samples of two patients, whose meshes had been explanted after >1 year in the body were examined by TEM. The "bark" was distinctly different ultrastructurally from the central core (Figure 25-28). There was detectably coarser graininess of the bark compared to the core material, where the grain size was larger towards the surface. The "bark" was either completely or partially separated from the core. It measured on average ~4 microns in thickness. The surface of the "bark" was irregular and had multiple cracks, where some cracks extended through the full "bark" thickness and either stopped at the "bark"-core interface or turned parallel to it.

The ultimate proof that the degradation and cracking of polypropylene occurs in the body was finding of cells wedged in the cracks. Human inflammatory cells migrate through tight spaces to deliver their immune response. In the case of bark cracks the cell remained wedged in a dead end fissure (Figures 29&30).

The surface defects were filled by tissue matrix and there were sites of collagen anchoring of to the surface (Figure 31). These indicated further that the degradation happens in the body, or in-vivo, as well as explains the adherence of the degraded outer layer to the tissue.

Mesh degradation alters polypropylene properties. The degraded layer has cracks showing its loss of elasticity. As a result, it introduces changes to polypropylene properties and contributes to mesh deformation and hardening. Additionally, degradation products may have a negative effect on the body.

1.4 MUCOSAL EROSIONS/ULCERATIONS AND POSTCOITAL BLEEDING

Mucosal ulcerations and postcoital bleeding commonly reported by the patients, whose explants were available for examination. To cause these symptoms a mesh needs to be in proximity to the surface, which is described in the clinical notes as superficial mesh location, "impending exposure". As was described earlier the mash migrates in the tissue, and can assume a superficial

position (Figure 3), or worst cases transmigrate through the mucosa (Figure 32). In mild cases of mucosal involvement the mesh is superficial, but is not exposed. Hardening of the mesh and scar plate provides additional factors of mucosal fragility over a superficially located hard mesh. In cases of transmigration, the ulceration can become a source of additional inflammation with pain and easy bleeding from the wound. These processes can be suspected clinically with complains of postcoital bleeding and can be readily seen by physical examination.

2. PATIENT SPECIFIC SUMMARIES OF CLINICO-PATHOLOGICAL CORRELATIONS

I reviewed the clinical information and deposition records of Ms. Hall and Ms. Smothers cases. Their mesh specific symptoms and complications can be correlated with the pathological findings I observed in explanted transvaginally placed Boston Scientific devices.

There is no available material for pathology assessment of the explanted mesh specimens of Ms. Hall and Ms. Smothers. Unfortunately, this situation is typical for mesh specimens, since they are not treated as important. In my consultation files, most cases either have not been examined by a pathology department or had "gross only" examination. In rare cases of performed microscopic examination only a small part is submitted and the assessment stops after a non-specific description of "foreign body with scarring and giant cell reaction". This vacuum created the situation where the morphological findings explaining the complications remained unrecognized.

Ms. Hall.

Clinical summary:

Ms. Hall was implanted with a Boston Scientific Obtryx Halo Sling in October 2006. In 2011 she reported feeling a foreign ("metal") object on the right side of the vaginal wall, pulling sensation on the right side of the pelvis, dyspareunia and postcoital bleeding. Physical examination showed mucosal mesh exposure. In 2011 she had an excision of the eroded sling parts from the left and right anterior vaginal walls. Physical examination in 2013 showed that the vagina barely admits 2 fingers to a depth of 8 cm, as well as tender transverse scar on the anterior vaginal wall with possible mesh underneath extending to the lateral wall. Her present complaints include constant pain in the right side of the vagina. Described as dull ache, also aggravated/intensifies with walking or similar activities. The area of removed mesh parts is painful to touch and during intercourse. Current symptoms also include nocturia, frequency urination, urgency and incontinence.

Clinico-pathological correlation:

Ms. Hall symptoms developed over time. Five years after implantation she had fully developed complications, which are commonly reported in the clinical records of the explant specimens I examined. The sensations of a foreign object and a pulling force clearly point to tissue distortions introduced by a deformed hardened mesh-scar fusion. As shown in section 1, the knitted polypropylene mesh curls the edges and deforms while in the body. The explanted slings transformed into firm deformed cord like structures, which are firmly fused to the tissue. After 5 years of body environment polypropylene has accumulated a layer of degradation bark, which is brittle and changes the original polypropylene qualities to add to the earlier pathological processes. Presently, physical examination reveals marked vaginal contraction with scarring. This further

points to tissue deformations and scarring introduced by the mesh.
The device is placed in the body to counteract the forces causing organ prolapse. At the stage of an established hardening and deformation, these forces act on the hard and deformed mesh with a reduced area of tissue attachment. The effect can be compared to straight pulling of the entire scalp hair vs. angled pulling on a bundle of hair. Ms. Hall reported asymmetry (right side) of the symptoms, which further indicates that the symptoms are caused by the non-native factors. There is a high degree of medical probability that hardening and deformation of the mesh caused the sensations of foreign object and pulling.

The next component of complications was pain, dull, intensified by walking or similar activities. As described in section 1, there are a number of mesh related changes, which provide mechanisms for pain development. Nerve ingrowth, entrapment, vascular compromise, muscle attachment, all can act in combination to produce chronic pain aggravated by movements. A separate component of pain, dyspareunia, can be related to the above mentioned mechanisms and additional direct contact with pressure, rubbing and pulling forces. In addition to ingrowth and entrapment in the deformity, superficial position of the nerves backing onto the hardened mesh can add to the risk of dyspareunia. Physical examination of Ms. Hall revealed superficial mesh position with overlying tender scar in addition to contracted vaginal walls. The contracted vaginal wall provide an additional mechanism for nerve and receptor irritation. The area of scarring was painful to the touch and during intercourse, which reflects the high probability of underlying mesh related pathological processes.

Ms. Smothers
Clinical summary:
Ms. Smothers was implanted with a Boston Scientific Obtryx Halo Sling in May of 2009. Later in 2009 she reported worsening incontinence to the point where she had to change a pad several times a day. Physical exam in March 2010, revealed an exposed foreign body in the suburethral area 2.5 cm proximal to the urethral meatus. Later in 2010 an exposed suture was removed and the sling was posteriorly cut, after which vaginal bleeding stopped and urinary symptoms improved. At the time of deposition she reported pain on direct contact: rubbing and dyspareunia; and pain in the vaginal area associated with certain movements: picking up objects from floor, moving in bed, and described it as shooting at the moment of movement. On physical exam in 2013 her vagina barely admits 2 fingers to a depth of about 8 cm Apex with nodularity and scar from the mid portion of the anterior vaginal wall to the right lateral side wall and at the posterior wall. Scarred parts were tender. Her current symptoms include urgency and hesitancy on urination, vaginal bleeding, internal pain in her lower abdomen and vagina, and dyspareunia.

Clinico-pathological correlation:
The first reported complications for Ms. Smothers was worsening incontinence. This can be explained by a pathological interaction of the mesh product with the urinary bladder and urethra. As shown in section 1, mesh penetrates deep into the bladder muscle and can affect the autonomous bladder innervation. At the same time, the mesh is subjected to the pulling force counteracting organ prolapse. Presence of the mesh within the wall, pulling forces acting on the wall through the attached mesh and the combined effect on autonomous bladder innervation can interfere with the normal bladder function. The reported alleviation of incontinence after a part of the mesh was removed reflects the pathological interaction described above. There is a high degree of probability that the urinary complications were caused by the mesh and bladder wall interaction.

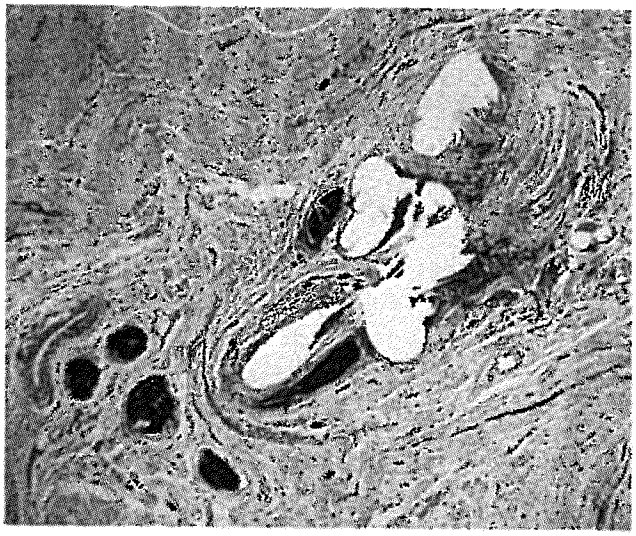
The next important complication for Ms. Smothers was pain with dyspareunia. As for Ms.

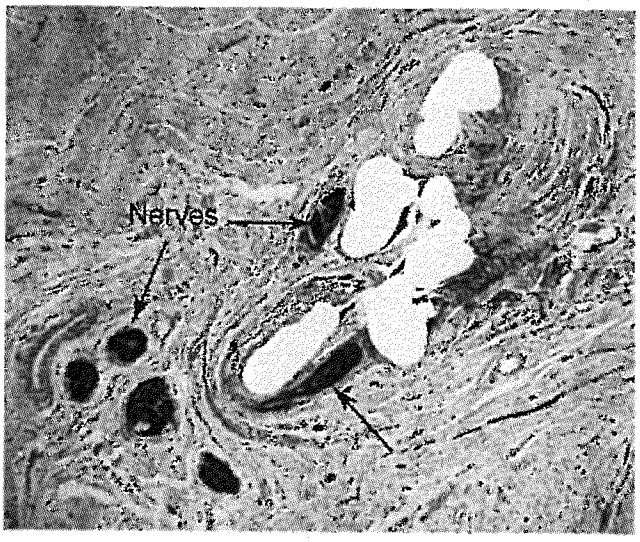
Hall and multiple other patients, the mesh introduces complex changes in the tissue, which provide variable mechanisms for pain development. Ms. Smother pointed to the association of pain with movements: picking up objects from floor, moving in bed, and described it as shooting at the moment of movement. The shown in section 1 nerve ingrowth, entrapment, muscle and tissue attachment to the mesh provide the pathological basis for this complication. An additional component of pain, dyspareunia, can be related to the above mentioned mechanisms as well as to an additional direct contact with associated variable forces. This forces act on a contracted vaginal wall, which was found during physical examination. The physical examination also showed tender scarring, which reflects the high degree of probability of the mesh related changes of scarring, deformity and nerve involvement. Vaginal bleeding indicates the probability of superficial mesh position, which adds to the vulnerability of superficially located nerves and receptors.

This correlation of clinical symptoms with pathological findings seen in explanted Boston Scientific mesh products, shows that there is high degree of medical probability that the complications experienced by Ms. Hall and Ms. Smothers developed due to the mesh design.

Microphotographs

(Where a labeled image is present, an unlabeled copy precedes it on the left. Mesh filaments are filled yellow in the labeled copies)





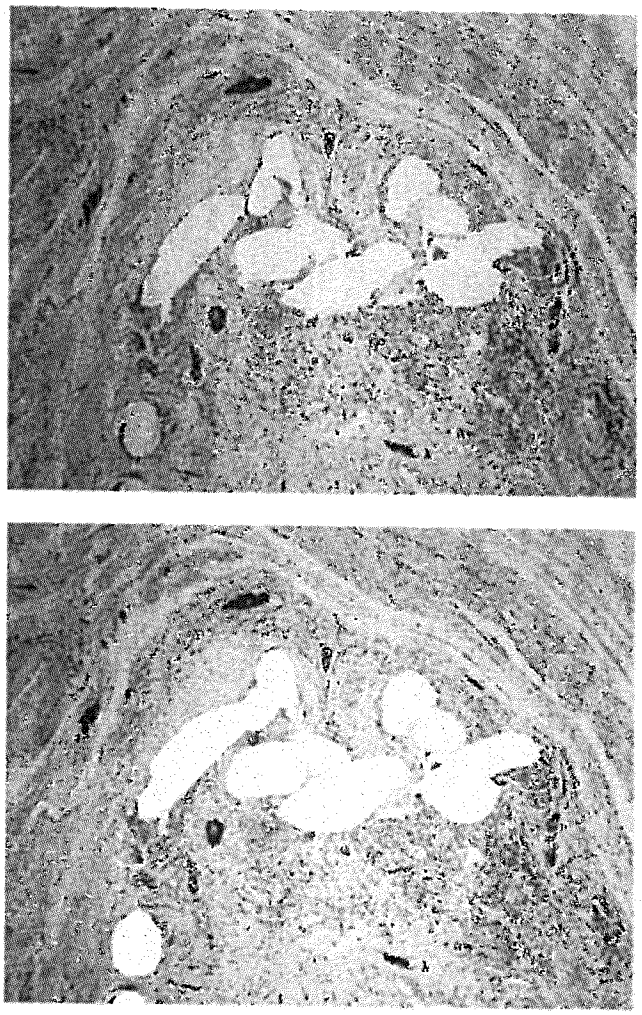
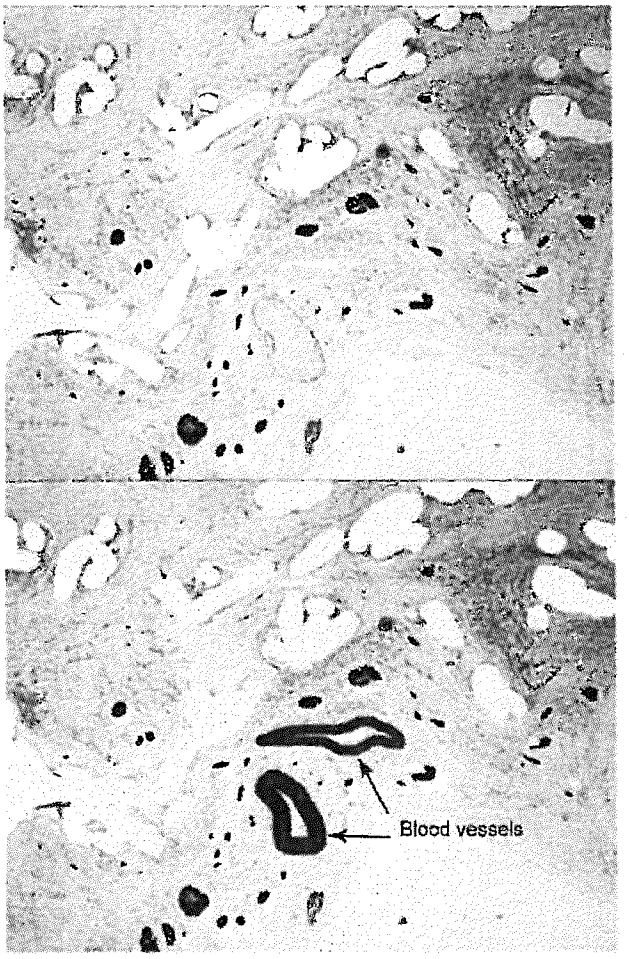
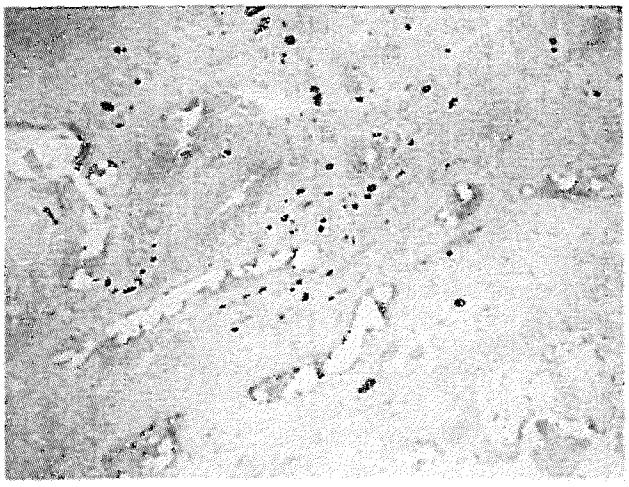


Figure 1. Examples of nerve ingrowth and entrapment

Immunostain against S100 protein, which is present in Schwann cells, stains peripheral nerves (nerves brown, all other tissue blue, mesh filaments transparent on the left and filled yellow on the right). The nerve branches enter between the mesh filaments and grow into the spaces of mesh structure. This is defined as nerve ingrowth since the spaces were created by the mesh placement into the body. These spaces are filled with dense collagenous scar, which fuses the nerves in their position – entrapment. In our study this phenomenon has been identified in 100% of explanted transvaginal meshes. All these patients had complains of pain.


Blood vessels



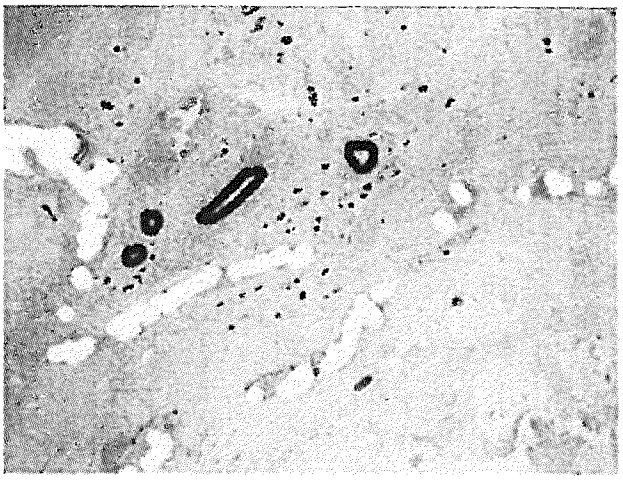


Figure 2. Examples of nerve entrapment by mesh deformation

The nerves (brown stain) are detected between the mesh folds. Unlike in Figure 1 this type of entrapment can occur without nerve ingrowth into the mesh structure. Pre-existent nerves can be wrapped by the deforming mesh. Note that the mesh is folding around vascular bundles in both cases. This indicates that the mesh is migrating and folding at the place of resistance.

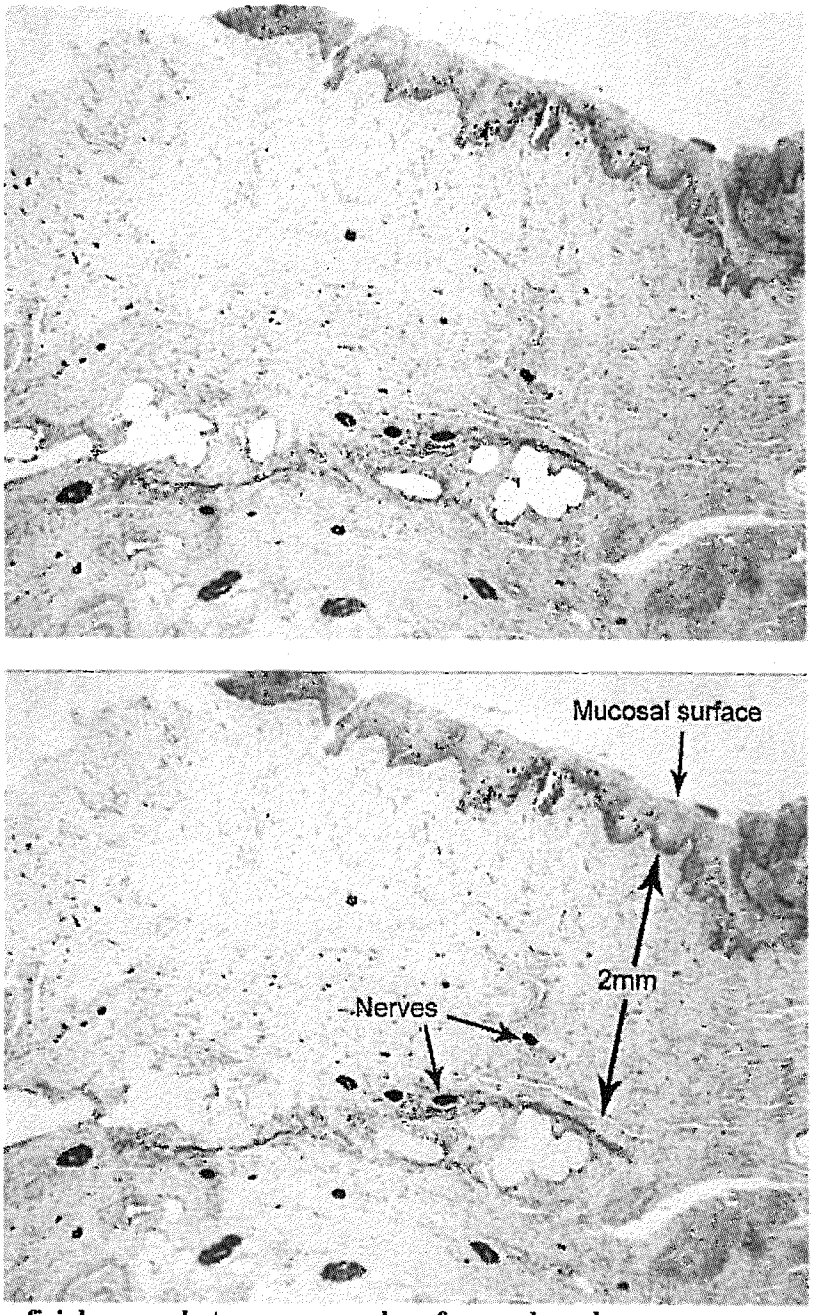


Figure 3. Superficial nerves between mucosal surface and mesh

The nerves are running on the mesh surface under thin layer of submucosal tissue. At this location external pressure (intercourse) on the mucosa can compress the nerves against hardened mesh.

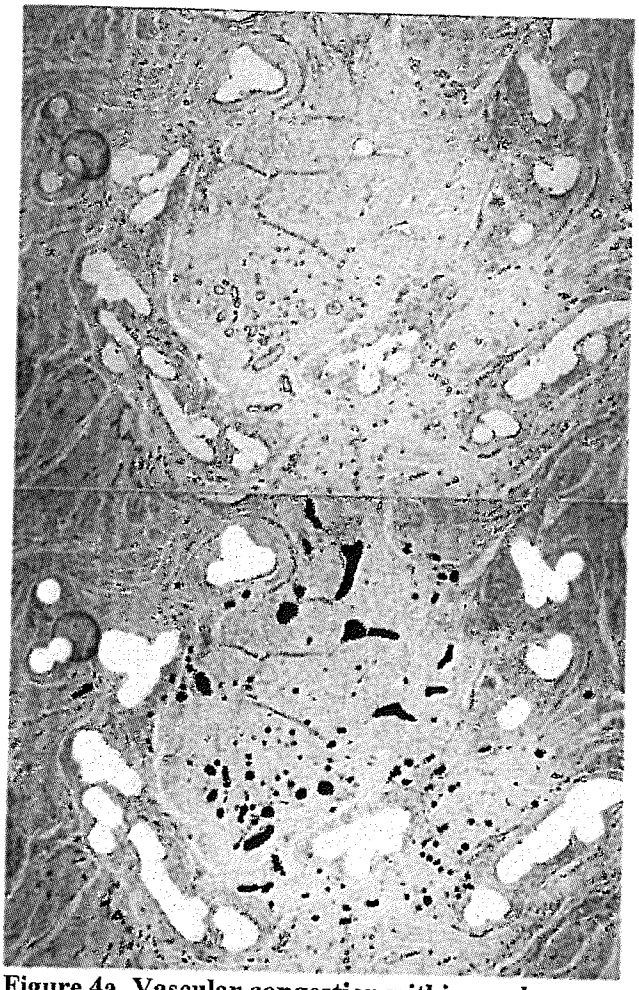


Figure 4a. Vascular congestion within mesh compartments
The vascular spaces within an enclosed compartment are congested and dilated. Vascular spaces are filled black on the right.

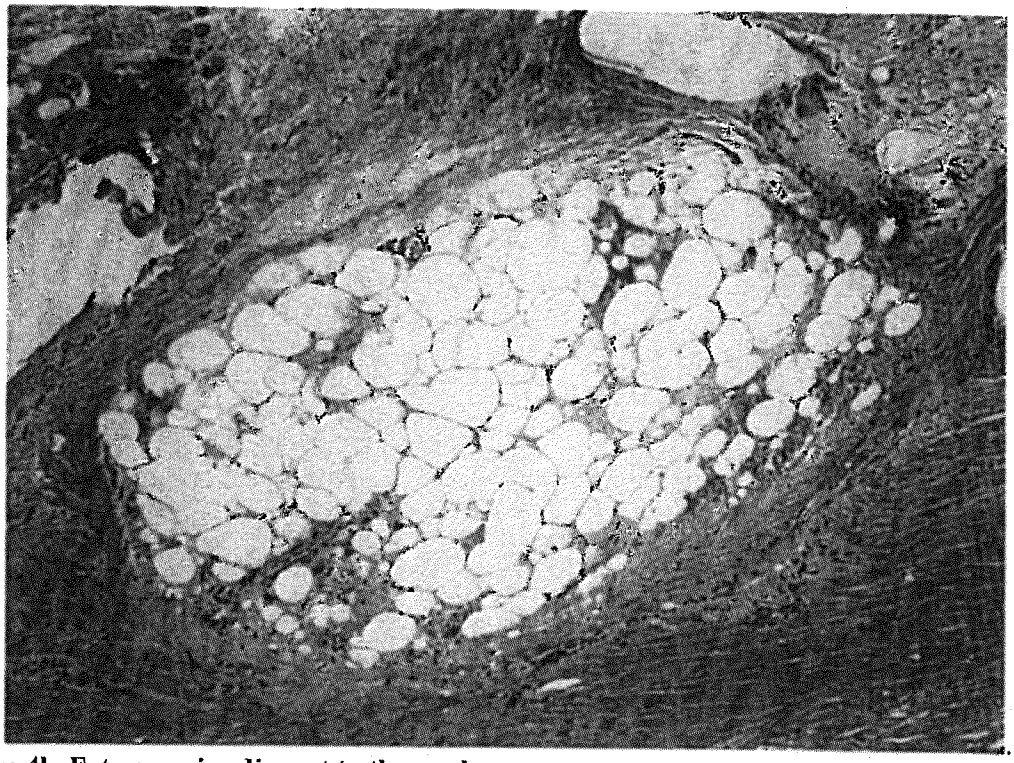
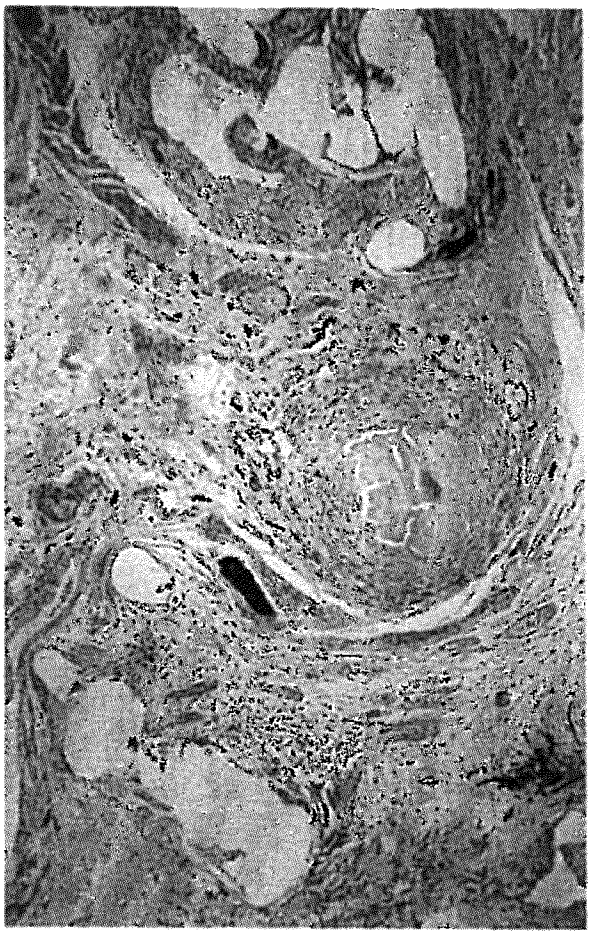


Figure 4b. Fat necrosis adjacent to the mesh
Fat is more sensitive to ischemia than scar tissue. While scar tissue becomes denser, the fat shows ischemic changes.



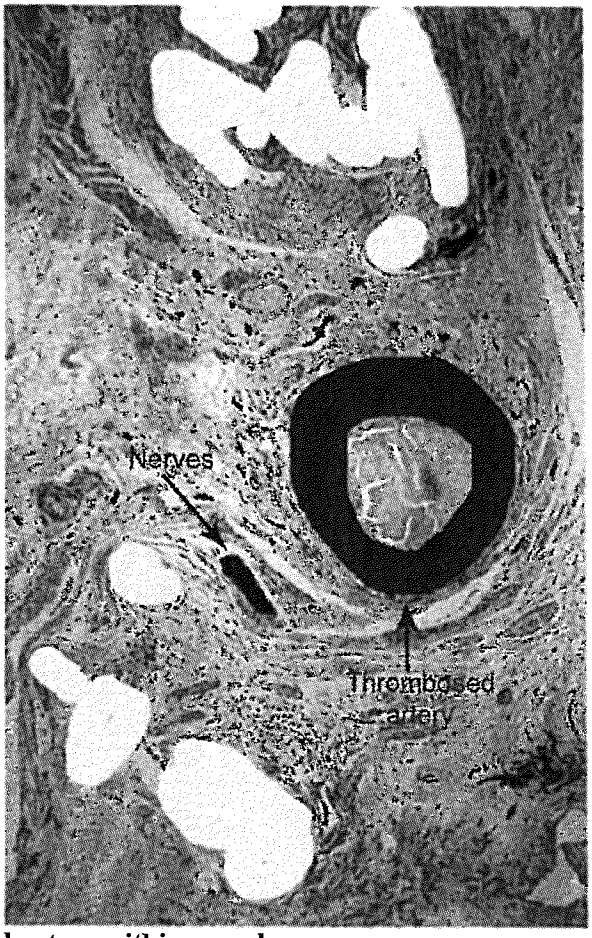


Figure 5a. Thrombosed artery within a mesh pore

A neurovascular bundle crosses a mesh pore where the artery became thrombosed. This caused repetitive or a single ischemic episode in the supply area of the artery.

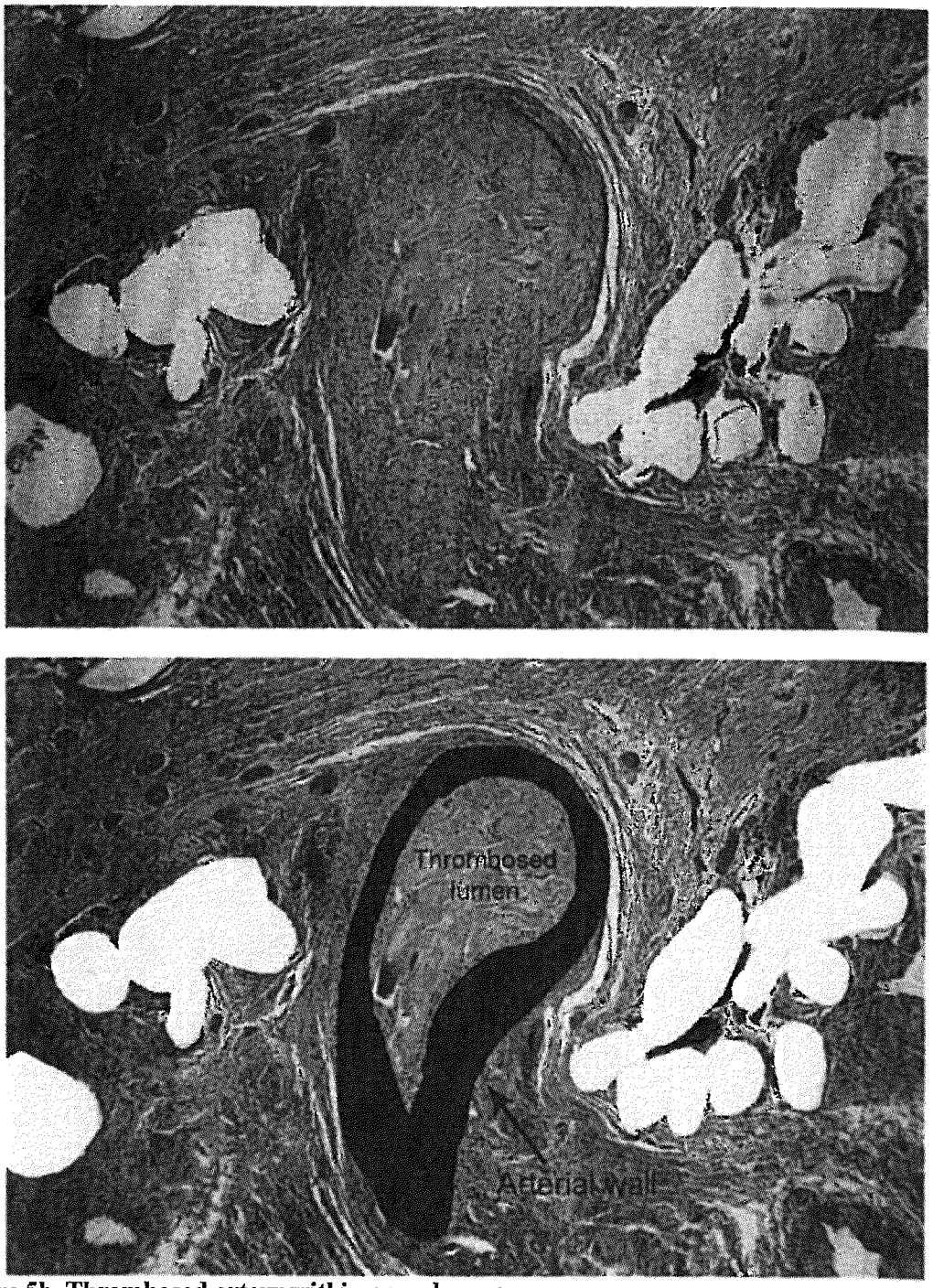


Figure 5b. Thrombosed artery within a mesh pore
The same artery as in 4a, routine haematoxylin & eosin stain (H&E).

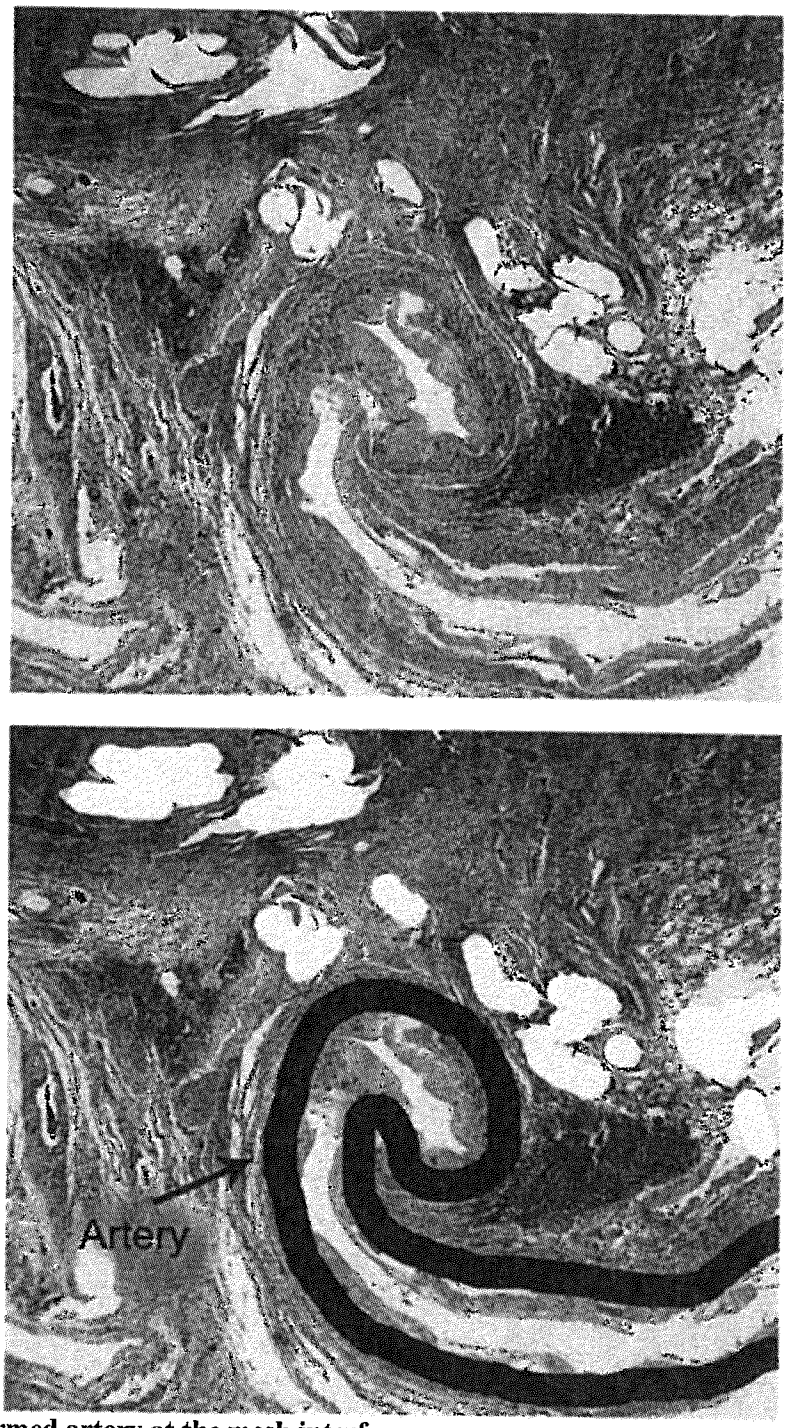


Figure 6. Deformed artery at the mesh interface
Another example of arterial involvement. This artery is not thrombosed, but is severely distorted, where the lumen can become closed with tissue movement. In this situation the patient is at risk for recurrent ischemic episodes.

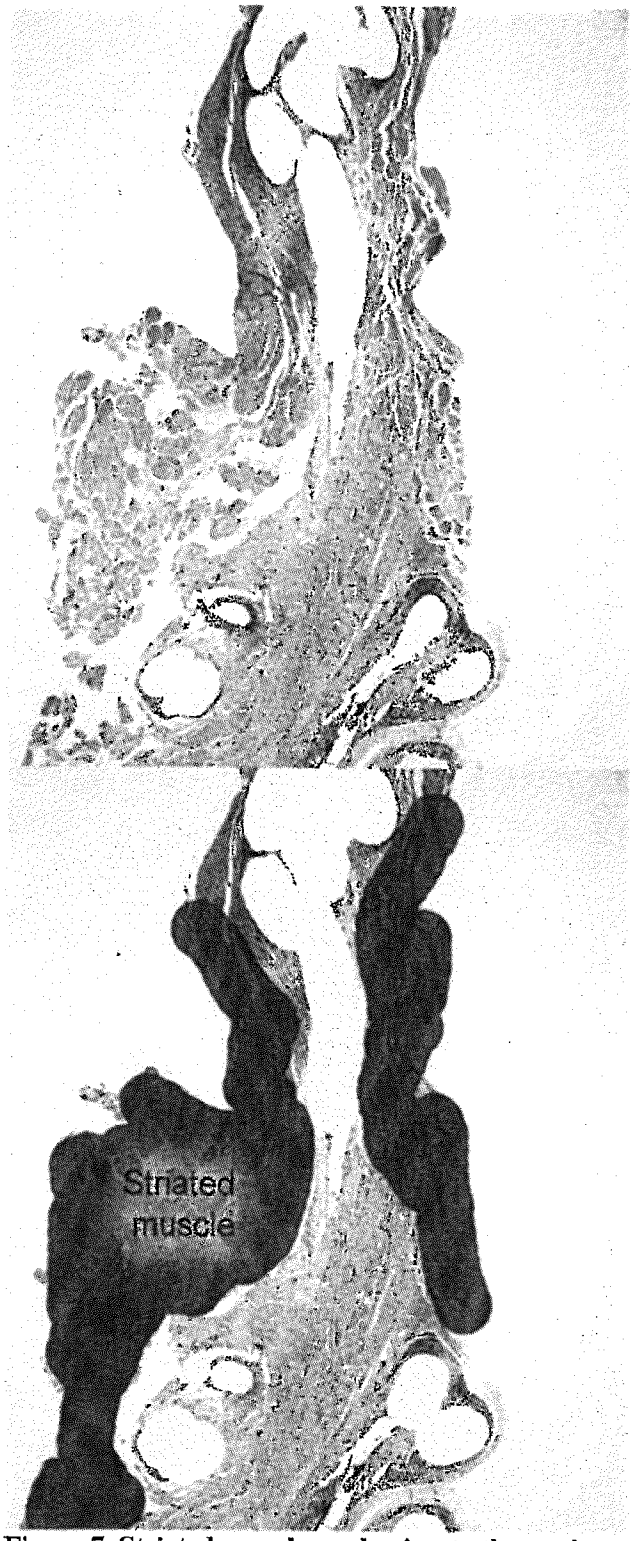
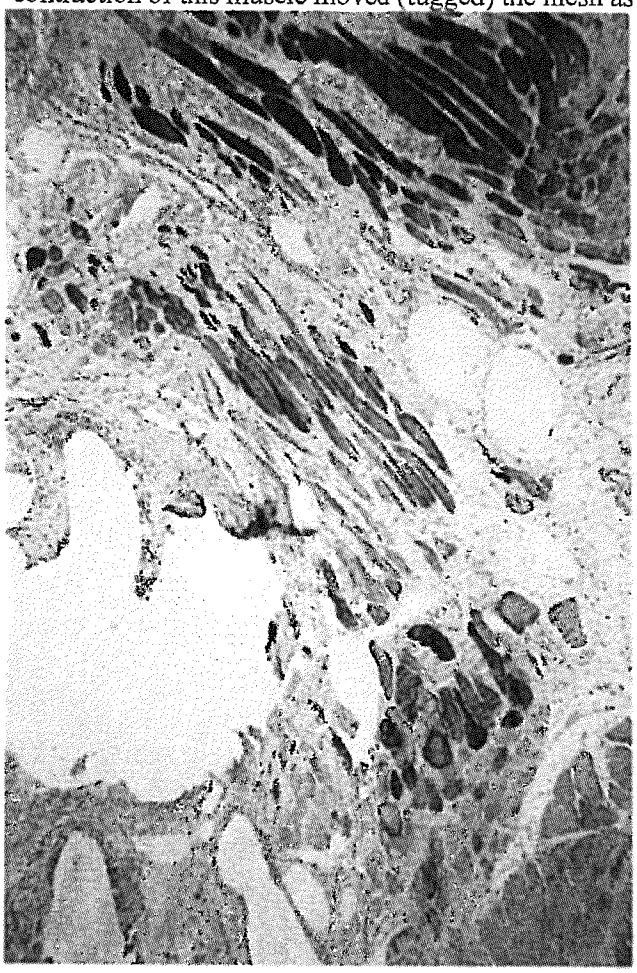


Figure 7. Striated muscle anchoring to the mesh

An example of striated muscle (red on the right) anchoring through the mesh. Striated

(skeletal) muscle provide conscious (voluntary) movements of our body. In this case movements, which are achieved by contraction of this muscle moved (tugged) the mesh as well.



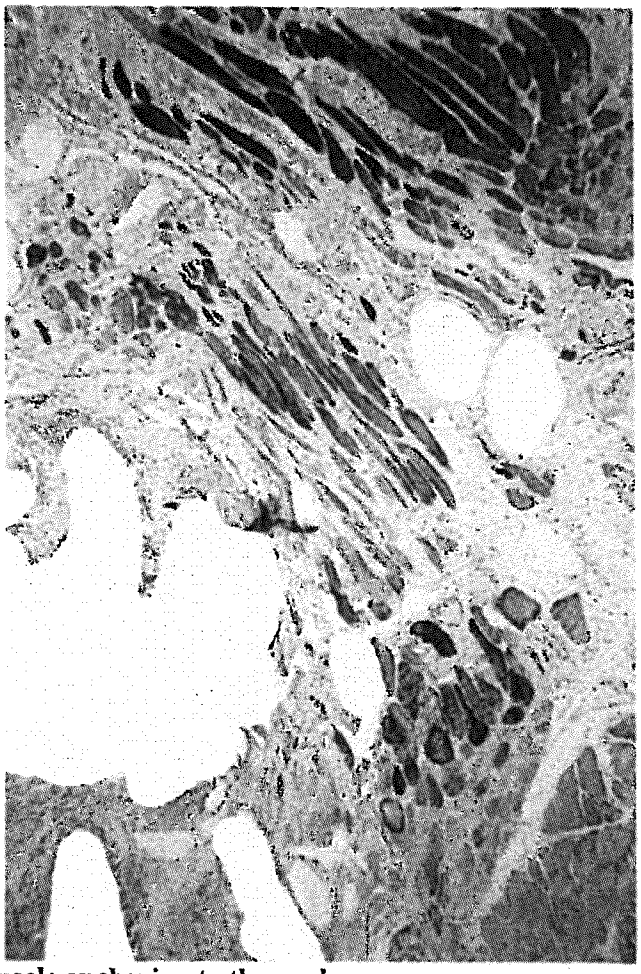


Figure 8. Striated muscle anchoring to the mesh
Muscle fibers stained for contractile protein desmin (brown). Note tight fit of the muscle bundle in the mesh pore.

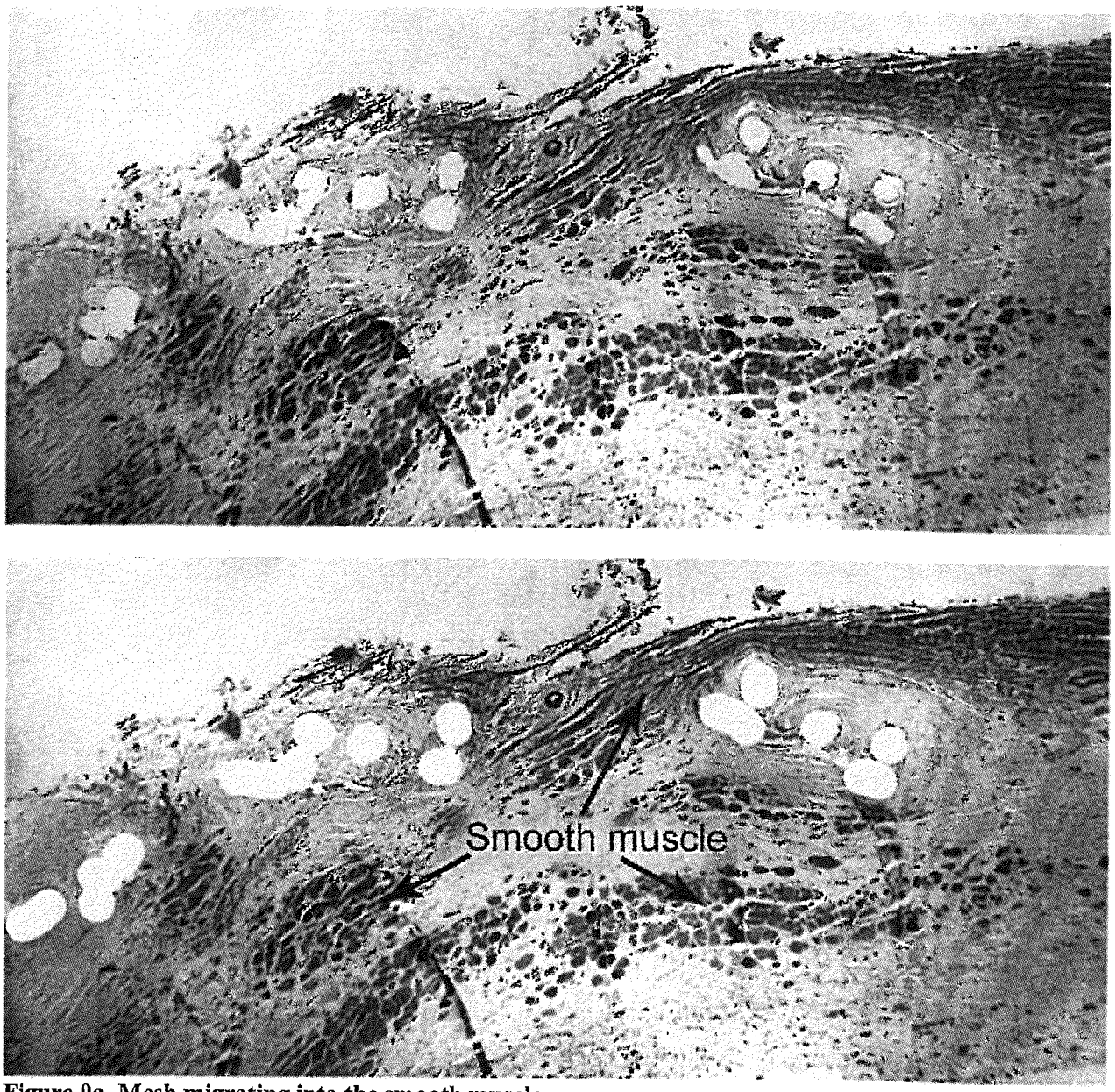


Figure 9a. Mesh migrating into the smooth muscle
Smooth muscle fibers are stained for contractile protein actin (smooth muscle specific, brown). Smooth muscle fibers in our body are non-voluntary. They act independently of our will and work inside internal organs to move bowel, empty urinary bladder, constrict blood vessels etc. At the mesh location the only organ, which can have bundles of this size is urinary bladder. The mesh migrated into the bladder wall, but has not eroded through the mucosa to be visible at cystoscopy.

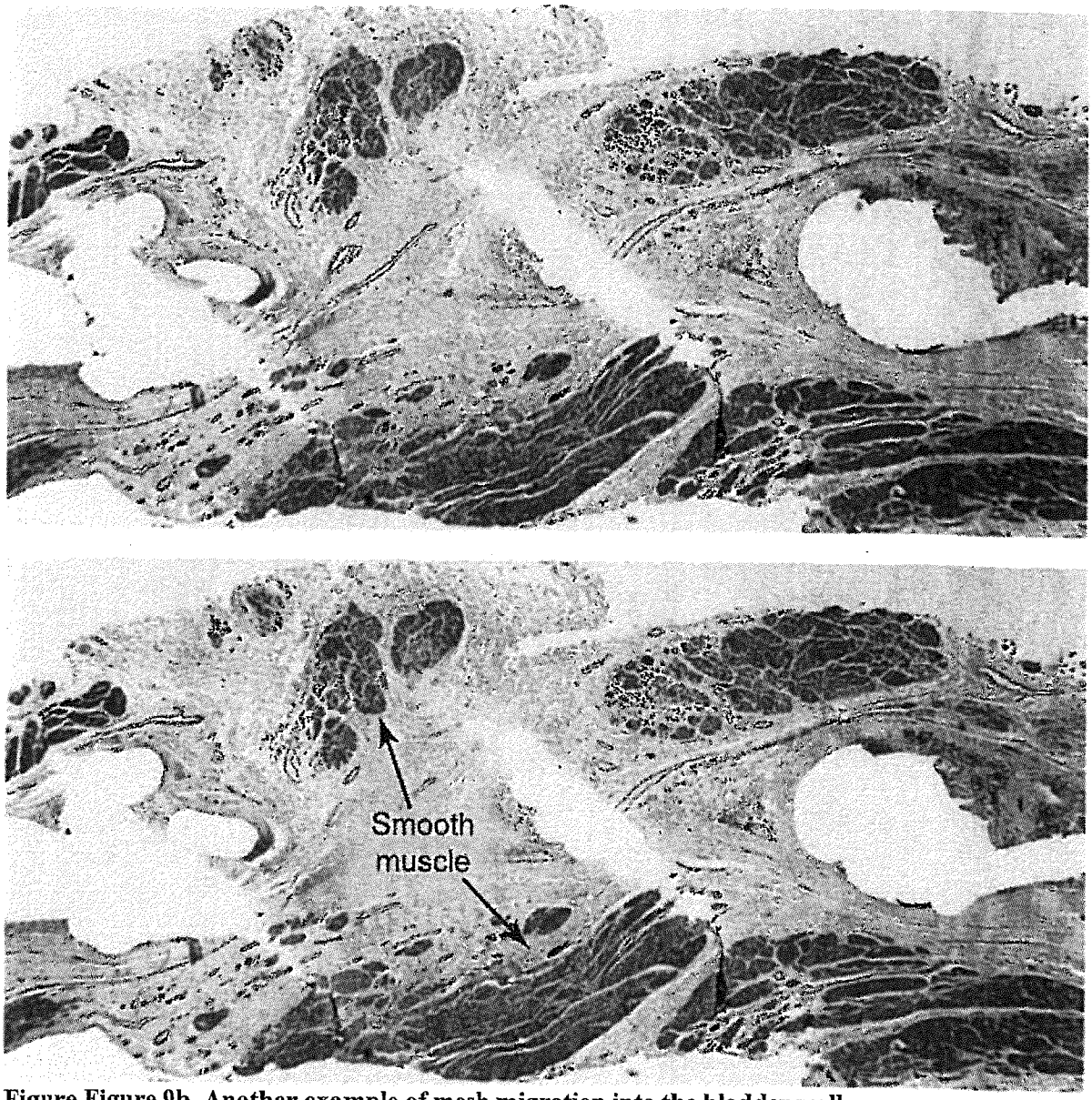
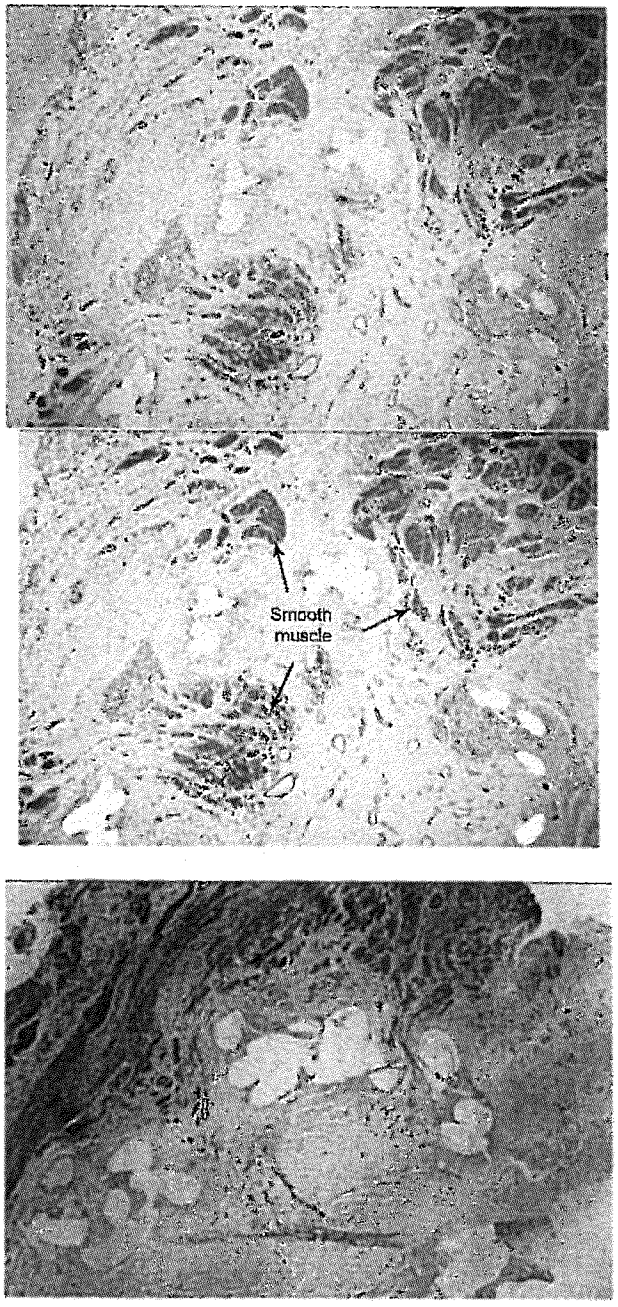


Figure Figure 9b. Another example of mesh migration into the bladder wall


Smooth
muscle

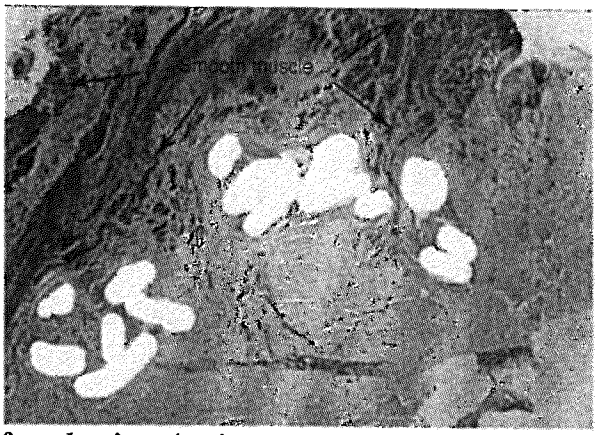


Figure 10. Examples of mesh migration into smooth muscle of different organization
The mesh in the top panel migrated into thick smooth muscle bundle consistent with bladder wall. The lower panel shows thinner bundles in more compact organization, which can represent urethra.

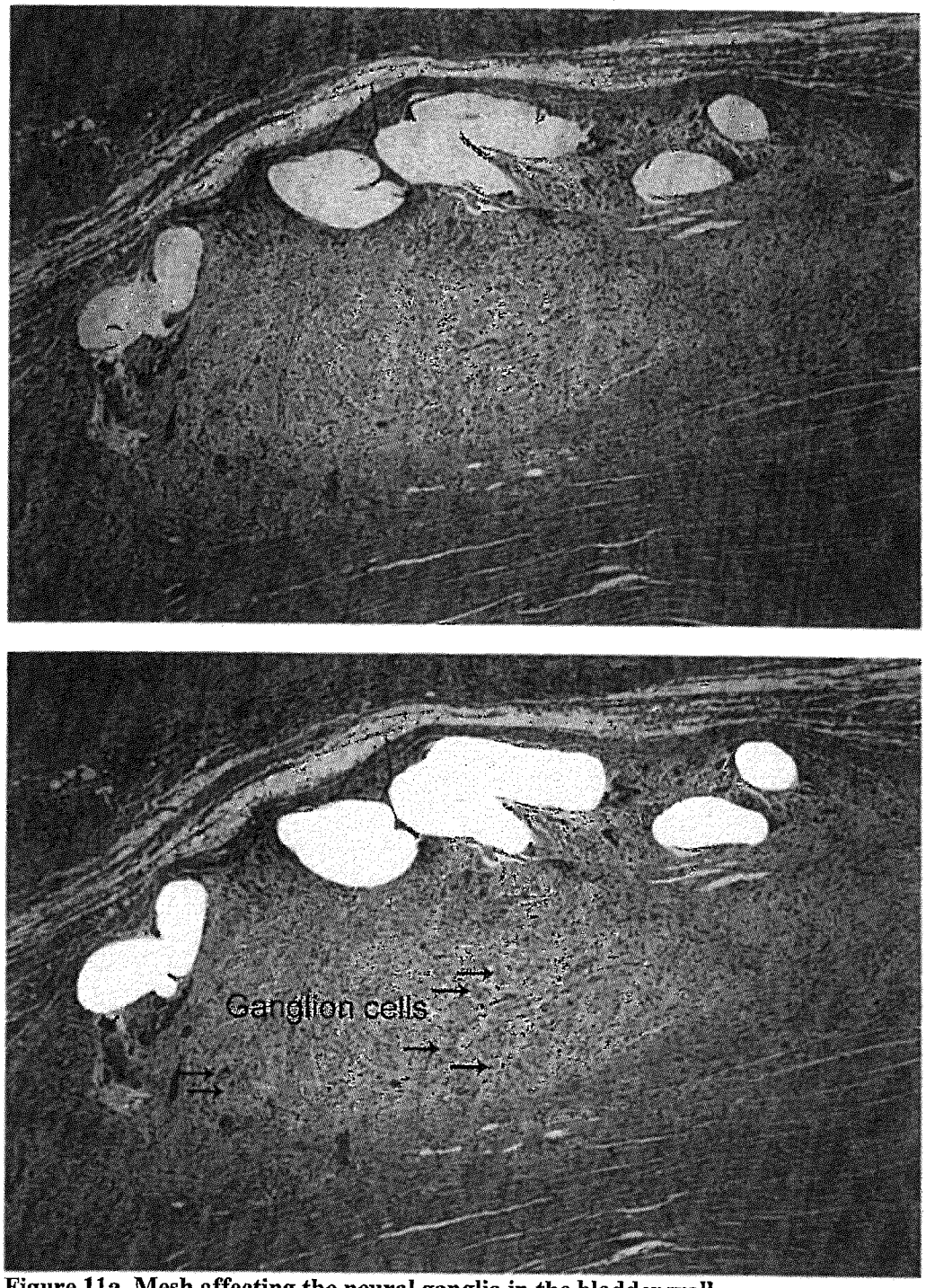
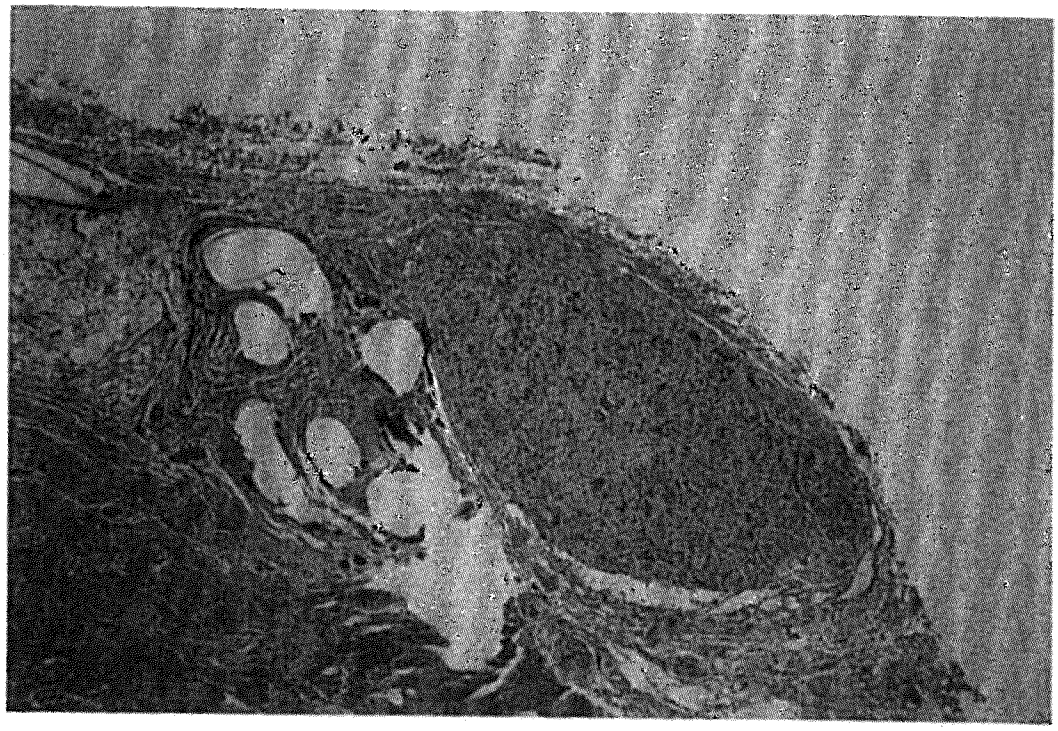


Figure 11a. Mesh affecting the neural ganglia in the bladder wall
Ganglion cells are neurons of autonomic, or independent from our will nervous system. The cells control the internal organs. They are either dispersed in the tissue or form a "control nodule" – ganglion shown in the picture.



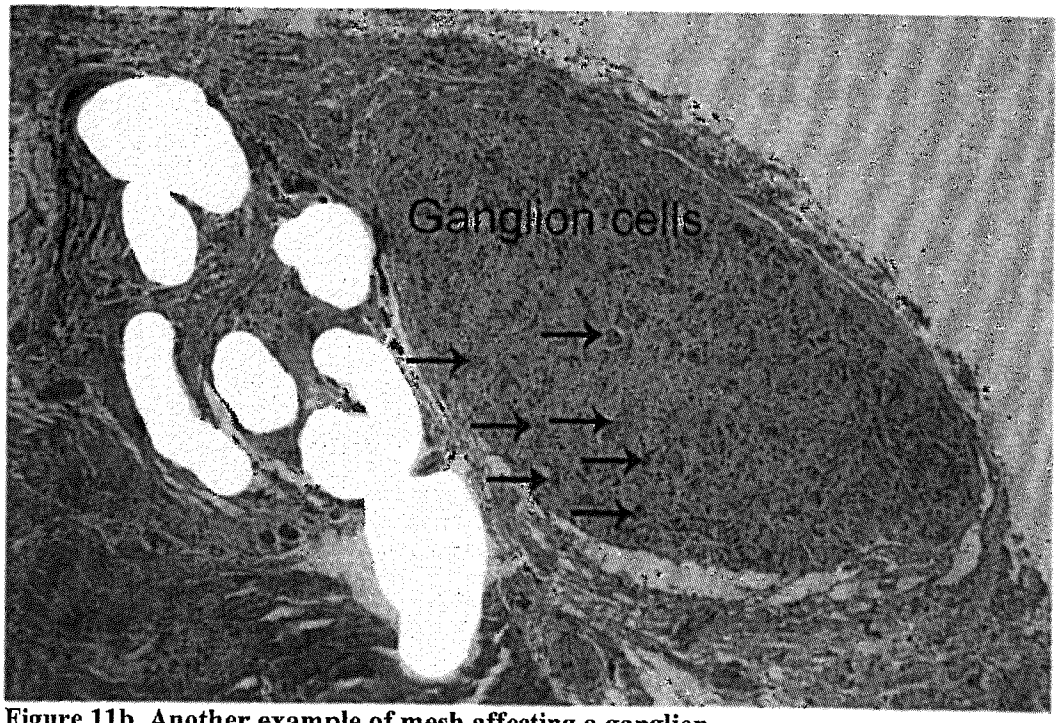


Figure 11b. Another example of mesh affecting a ganglion

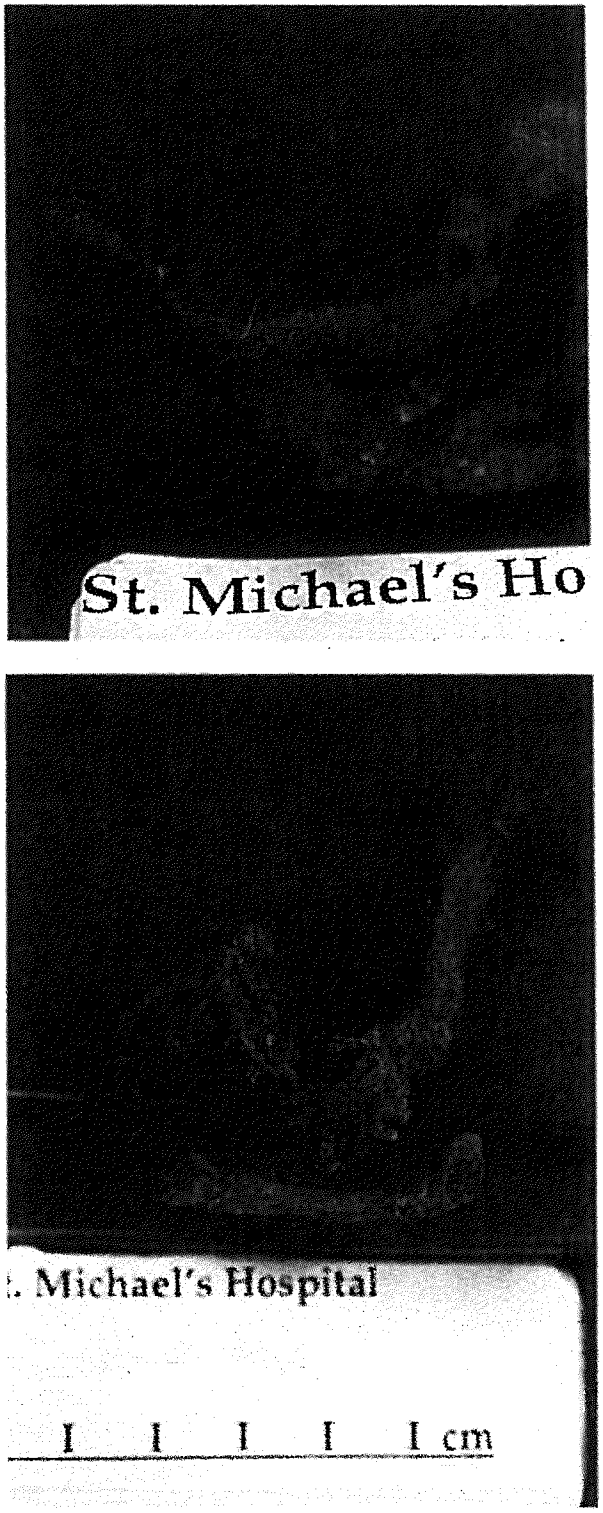


Figure 12. Explanted Boston Scientific meshes.
The mesh edges rolled-in. The tape like parts formed a cord-like roll.

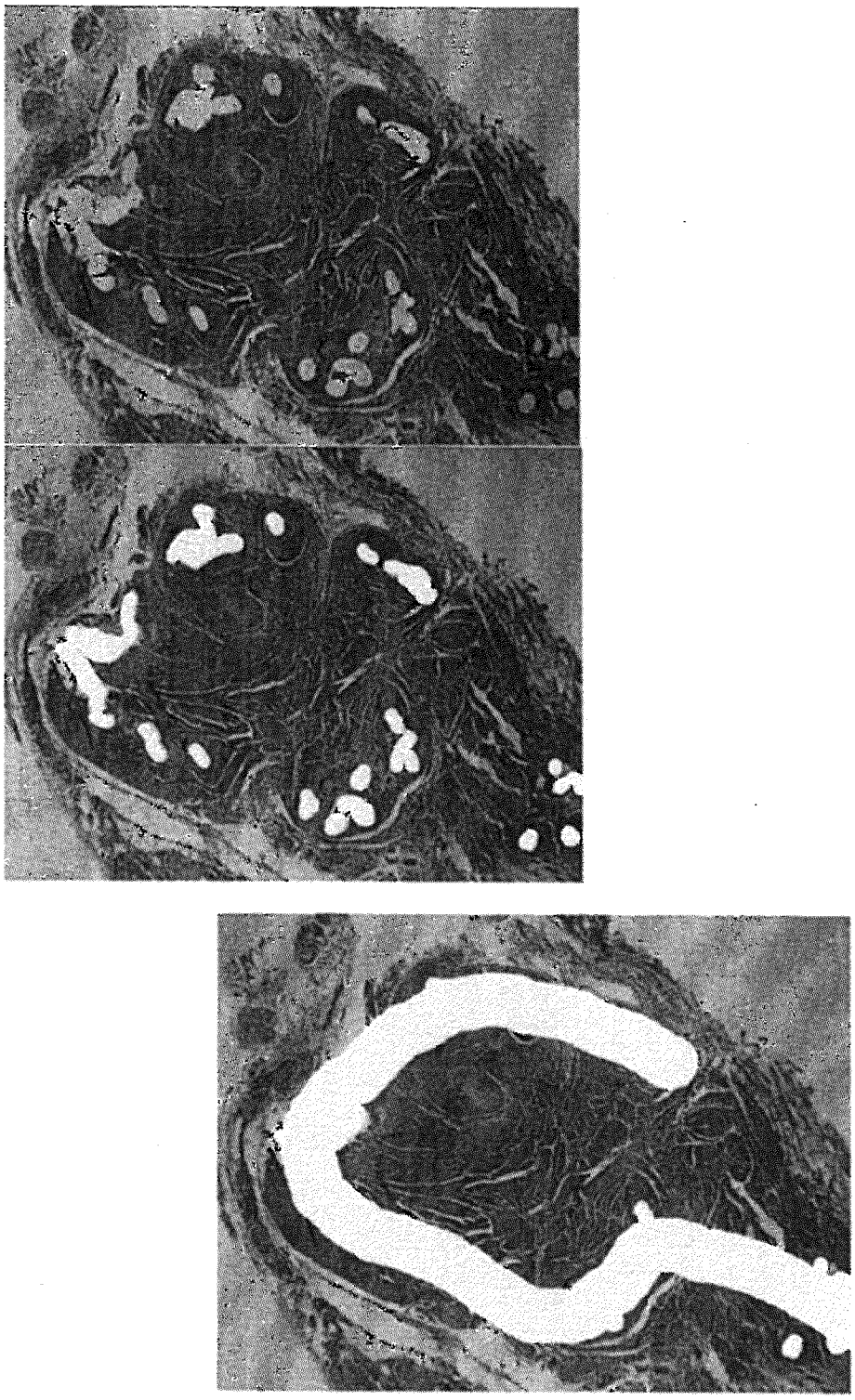


Figure 13. Curling edge deformation

The mesh edges curl like edges of knitted fabric. The lower panel has solid yellow band

following the mesh plane. Note that the mesh is fused in this shape by scar tissue.